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2022-11

Hemminki , J , Försti , A , Hemminki , A & Hemminki , K 2022 , ' Survival trends in solid cancers in the Nordic countries through 50 years ' , European Journal of Cancer , vol. 175 , pp. 77-85 . https://doi.org/10.1016/j.ejca.2022.08.015

http://hdl.handle.net/10138/351277
https://doi.org/10.1016/j.ejca.2022.08.015

European Journal of Cancer 175 (2022) 77–85

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Survival trends in solid cancers in the Nordic countries through 50 years

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Received 13 June 2022; received in revised form 9 August 2022; accepted 10 August 2022
Available online 9 September 2022

KEYWORDS
Prognosis;
Periodic survival;
Treatment;
Cancer control

Abstract ***Aims:*** Global survival studies in cancer have generally shown favourable development, but studies over extended periods on populations for which medical care is essentially free of charge are lacking.
Methods: We analyse relative 1- and 5-year survival in all solid cancers in Denmark, Finland, Norway and Sweden through a 50-year period (1970–2019) using the NORDCAN database.
Results: The most recent survival results showed three types of patterns. Cancers of very good survival (5-year survival ~90%) included common cancers of the breast and prostate, as well as melanoma. The second pattern, which included the largest number of cancers, showed 1-year survival of over 80% and a drop of 10–20 % units in 5-year survival. The third group consisted of eight fatal cancers, sharing poor 5-year survival (around 20%). The 50-year improvement in 1-year survival was largest (30–50 % units) in kidney, brain, gallbladder and liver cancers, and (~30%) in colon, small intestinal, lung, pleural, pancreas and ovarian cancers. Improvements in 5-year survival were highest (40–50 % units) in prostate and kidney cancers but remained at 10–20 % units for the eight fatal cancers. Survival showed significant sex preferences for a few cancers.
Conclusions: The analysis over a half-century confirms the progress in 'real-world' cancer control, and in 84% of patients 5-year survival was >60%. Metastases remain a challenge,

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https://doi.org/10.1016/j.ejca.2022.08.015

placing the emphasis on early detection before metastasis occurs. Novel therapies, such as immunotherapy which has curative potential even against metastatic disease, are needed.

1. Introduction

Improving cancer survival without compromising the quality of life is the ultimate goal of oncological care. Survival in a particular cancer is influenced by many factors including demographics (age, sex, performance status) and cancer-related (stage, grade) factors, comorbidities, treatment, overall care during and after treatment and lifestyle and social factors. Although overall survival in many cancers has improved over the past years, the reasons for favourable development may have many interpretations [1–4]. Among individual cancers for which high cure rates were achieved over a short interval, success has been ascribed to therapy and supportive care [5–7]. Testicular cancer is a classic example of a survival success in solid cancers, achieved by rational utilisation of combination chemotherapy, with the integration of medical and surgical specialties enabled the success [7]. A more recent success has been the rectal cancer, for which the improvements have been associated with refined surgical techniques in combination with preoperative radiotherapy [8–10]. Therapies for these success stories were optimised in clinical randomised trials conducted in specialised centres.

When population-level survival is assessed, high-level cancer registries are an optimal setting. Long-term follow-up will help in the interpretation of survival changes and the access of the population to basic health care free of charge would minimise biases due to economic affordability. The Nordic cancer registries fulfil these requirements, and they are the oldest national cancer registries in the world and cover practically all cancers without loss to follow-up [11]. The Nordic cancer registries have delivered aggregated data to the NORDCAN database, which has been a rich source of epidemiological analyses including a set of survival studies covering 1964–2003 (https://www.ancr.nu/cancer-data/cancer-survival/acta-oncologica-2010). Recently, the updated NORDCAN became available at the International Agency for Cancer (IARC) website (https://nordcan.iarc.fr/en/database#bloc2) enabling survival studies through 2019.

We will assess the relative 1- and 5-year survival in solid cancers from Denmark (DK), Finland (FI), Norway (NO) and Sweden (SE) from 1970 to 2019. These countries have organised health care largely in a similar way and with a principle of access with minimal direct costs to patients. However, health care resources depend on the countries' economic prosperity and the share of the gross national product used for health care. As guidance, health care expenditure per capita in 2000 was $2496 (8.8%) in DK, $1723 (7.1%) in FI, $2949 (7.7%) in NO and $2173 (7.3%) in SE (www.macrotrends.net). Between 1970 and 2019, life expectancy increased in FI by 11.6 years and in other countries by 8 years. We show data on 1- and 5-year survival in 1970-74 and 2015–19 and survival difference between these periods.

2. Methods

The data used originate from the NORDCAN database, which is a compilation of data from the Nordic cancer registries as described [11,12]. The database was accessed at the IARC website (https://nordcan.iarc.fr/en/database#bloc2). We included only solid cancers in the analysis, as listed in Supplementary Table 1 with their International Classification of Diseases (ICD) version 10 codes. Of note, the code for brain cancer includes both malignant (such as glioma) and indolent (such as meningioma) tumours, and meningiomas are more common in females compared with males [13]. The code for gallbladder cancer includes also cancers of extrahepatic bile ducts, which for men are approximately as common as gallbladder cancer; for women, gallbladder cancer is the dominant type [14]. Borderline ovarian cancers should not be included, but if these were systematically excluded is not known [11,15]. Some rare or undefined cancers such as anal, 'other uterine' and some endocrine tumours were not included.

Survival data were available from 1970 through 2019, and the analysis was based on the cohort survival method for periods from 1970 to 2014, and a hybrid analysis combining period and cohort survival in the last period 2015–2019, as detailed [12,16]. Age-standardised relative survival was estimated using the Pohar Perme estimator [17]. Age-standardisation was performed by weighting individual observations using external weights as defined at the IARC web site [18]. National general population life-tables stratified by sex, year and age were used in the calculation of expected survival. Death certificate only cases were not included. Patients of 90 years or older were excluded. Groups were analysed if a minimum of 30 patients were alive at the start and with

a minimum of 3 patients in any one of age-groups used for weights.

3. Results

The numbers of cancer patients in DK, FI, NO and SE are shown for the period 2015–19 in Supplementary Table 2.

Relative 1-year (top four symbols) and 5-year (bottom four symbols) survival of all male solid cancers is shown in Fig. 1, and the underlying data are tabulated in Supplementary Table 3. Cancers are ordered based on SE 1-year survival, and this order is maintained in the subsequent tables to help comparisons. There are essentially three clusters of cancer survival. The left cluster includes cancers of excellent 1-year survival for which mortality remains low up to 5 years. The middle is occupied by the large majority of cancers for which the difference between 1- and 5-year survival ranges from 10 to 20 % units. On the right, for eight fatal cancers, the difference between 1- and 5-year survival is 30 % units or more, and 5-year survival is around 20% or even less.

Relative 1- and 5-year survival for female solid cancers is shown in Fig. 2, and the underlying data are tabulated in Supplementary Table 4. Female cancers are ordered to the extreme right. The patterns are quite similar to the male ones, and, for example, the eight fatal cancers are the same for both sexes. Among female cancers, breast cancer has an excellent survival up to 5 years while endometrial and cervical cancers show separate clustering of 5-year survival. Ovarian cancer shows >80% 1- year but only 50% 5-year survival.

Survival differed with sex in some cancers (significant differences are shown in Supplementary Table 3 for male advantages and Supplementary Table 4 for female advantages by underlining). Male bladder cancer 1- and 5-year survival was better than those for women in all countries. Female brain and lung cancer 1- and 5-year survival was better than those for men in all countries. Female 5-year survival in skin cancer and melanoma was better than male survival in all countries, and for colorectal, colon, oral and stomach cancers, it was better than male survival in three of four countries.

In general, country-specific differences were small, but they showed some consistency. Counting the country with best male 5-year survival among 25 cancer types with information from each country, NO showed best survival for 13 cancers, DK for 5 cancers, SE for 5 cancers and FI for 1 cancer (bolding in Supplementary Table 3). The top ranks in 29 female cancers were for NO in 13, DK in 8, SE in 5 and FI in 3 cancers (bolding in Supplementary Table 4). In NO, the best ranking was reached for the same eight male and female cancers, while in DK and SE sex concordance was achieved for

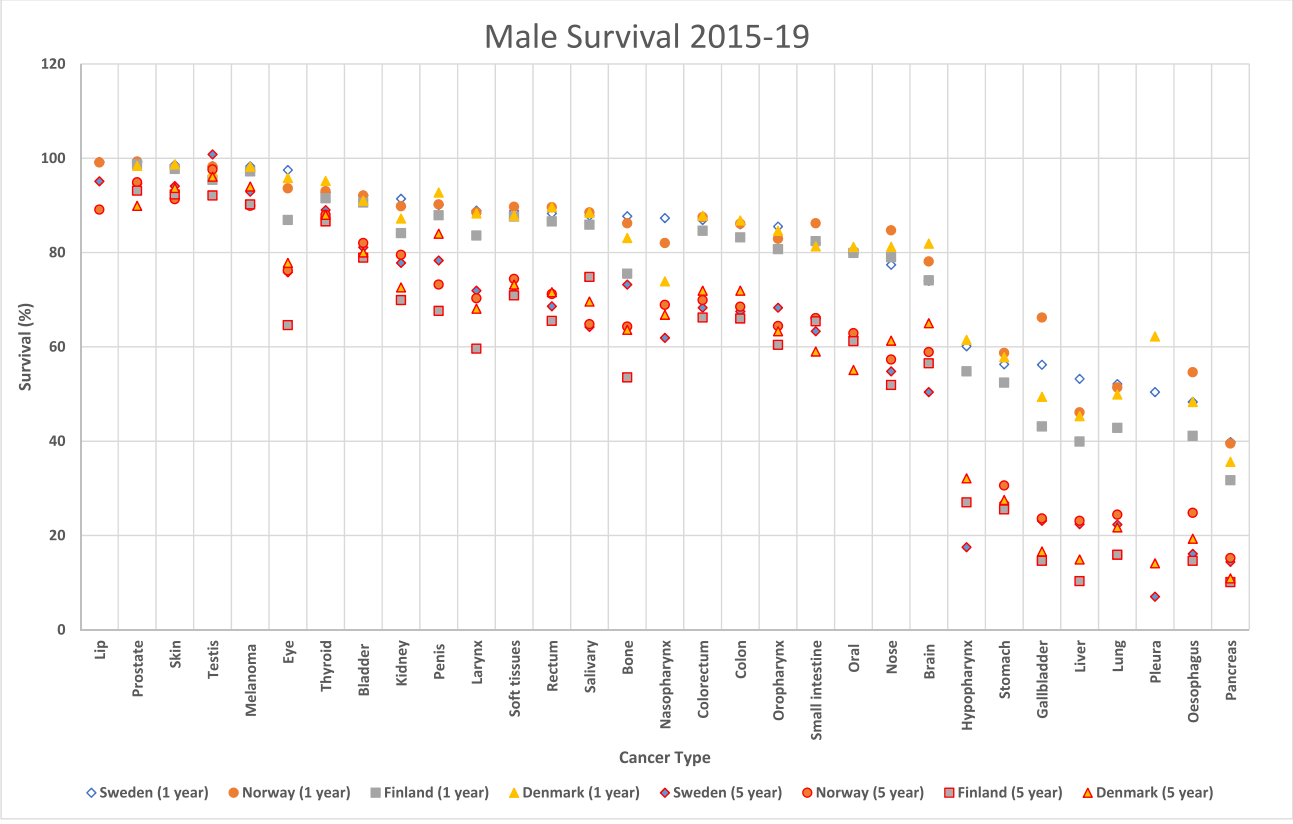

Fig. 1. Relative 1- (top symbols) and 5-year (bottom symbols) survival in Nordic men in 2015-19.

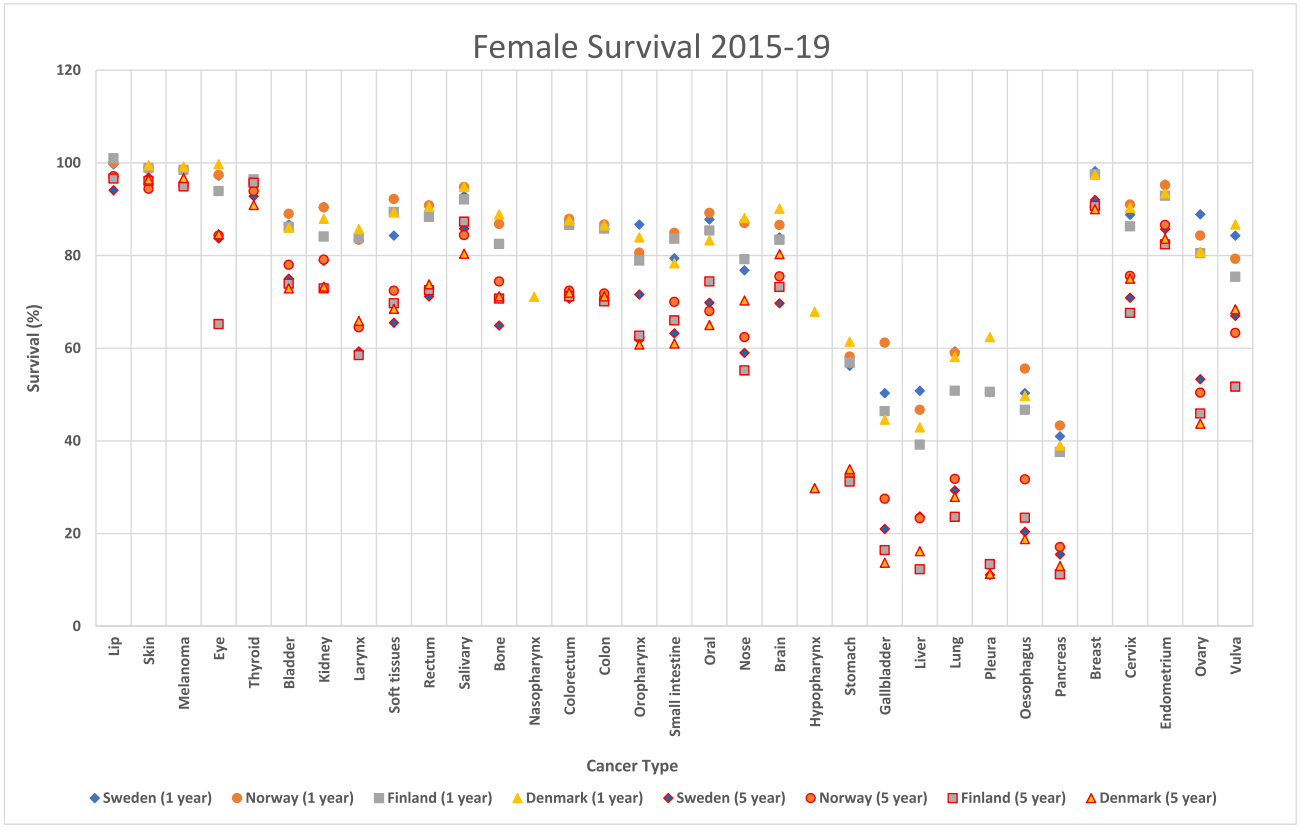

Fig. 2. Relative 1- (top symbols) and 5-year (bottom symbols) survival in Nordic women in 2015-19.

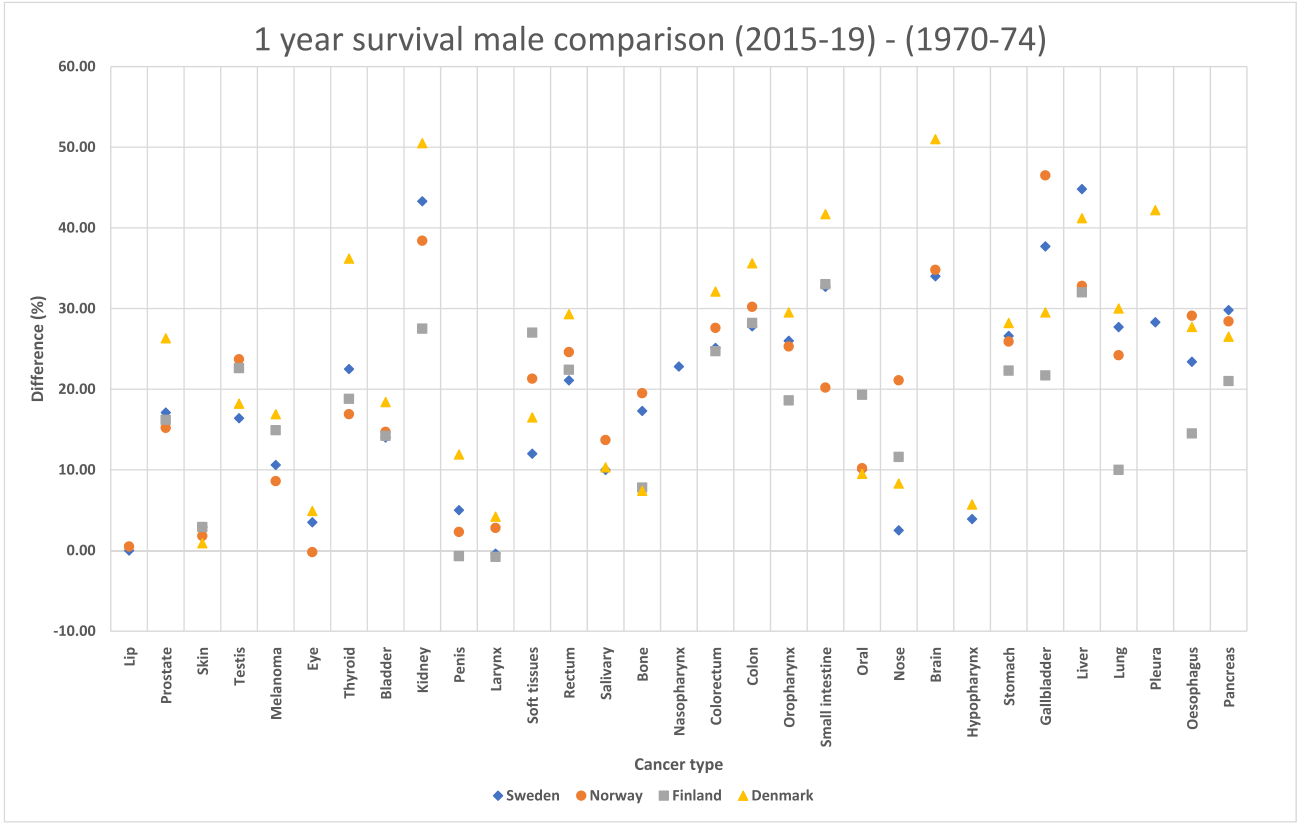

Fig. 3. Difference in 1-year relative survival (in % units) for Nordic men between 1970-74 and 2015–19.

two cancers. NO had the best 5-year survival for many of the most fatal cancers, such as those in the gallbladder, lung, oesophagus and pancreas, some with large margins to the other countries.

The periodic difference from 1970 to 74 and 2015–19 in male 1-year survival is shown in Fig. 3, with data in Supplementary Table 5. For indolent cancers of the lip, skin (non-melanoma), eye, penis and larynx, no improvement was evident in the course of 50 years. In contrast, large, about 40% unit improvements were observed for cancers of the kidney, brain, gallbladder, liver and pleura. For some cancers, such as kidney and gallbladder cancers, country-specific differences were conspicuous.

Periodic improvement for female 1-year survival is depicted in Fig. 4 (with data in Supplementary Table 5), with many similarities to the male data. Among female-specific cancers, the improvement was mostly 10% but more, 30% in ovarian cancer. The large country-specific differences were noted for kidney cancer, and the order was the same as in male kidney cancer.

Periodic improvement from 1970 to 74 and 2015–19 in male 5-year survival is shown in Fig. 5, with data in Supplementary Table 5. For prostate and kidney cancers, the survival gain was 50 % units, and for testicular, rectal, oropharyngeal, small intestinal and brain cancers and for melanoma gains in many countries reached 40%. Improvements were marginal for cancers of good survival, such as skin, penile and laryngeal cancers, and they were modest 10–20% for the eight most fatal cancers (accounting for 17.0% of male solid cancers). Notably, the country-specific difference was no longer large for kidney cancer, but for 5-year survival, these were large for soft tissue, small intestinal, oral and nasal cancers.

Survival improved markedly for kidney and brain cancers also for women (Fig. 6, with data in Supplementary Table 5). Overall, female cancers showed less country-specific heterogeneity than male cancers. The cancers of poor survival were the same as for men and accounted for 15.4% of female solid cancers. Among female-specific cancers, the improvement in breast cancer was 30%, and in ovarian cancer, it was 20%, both gains were very similar in all countries; more heterogeneity between countries was seen for cervical and vulvar cancers.

Country-specific increases in 5-year survival differences between 1970–74 and 2015–19 could be assessed for 24 male cancers with data for all four countries (Supplementary Table 5). DK had 9, NO 10, FI 4 and SE 0 largest improvements, and for one cancer DK and FI achieved an equal improvement. For 28 female

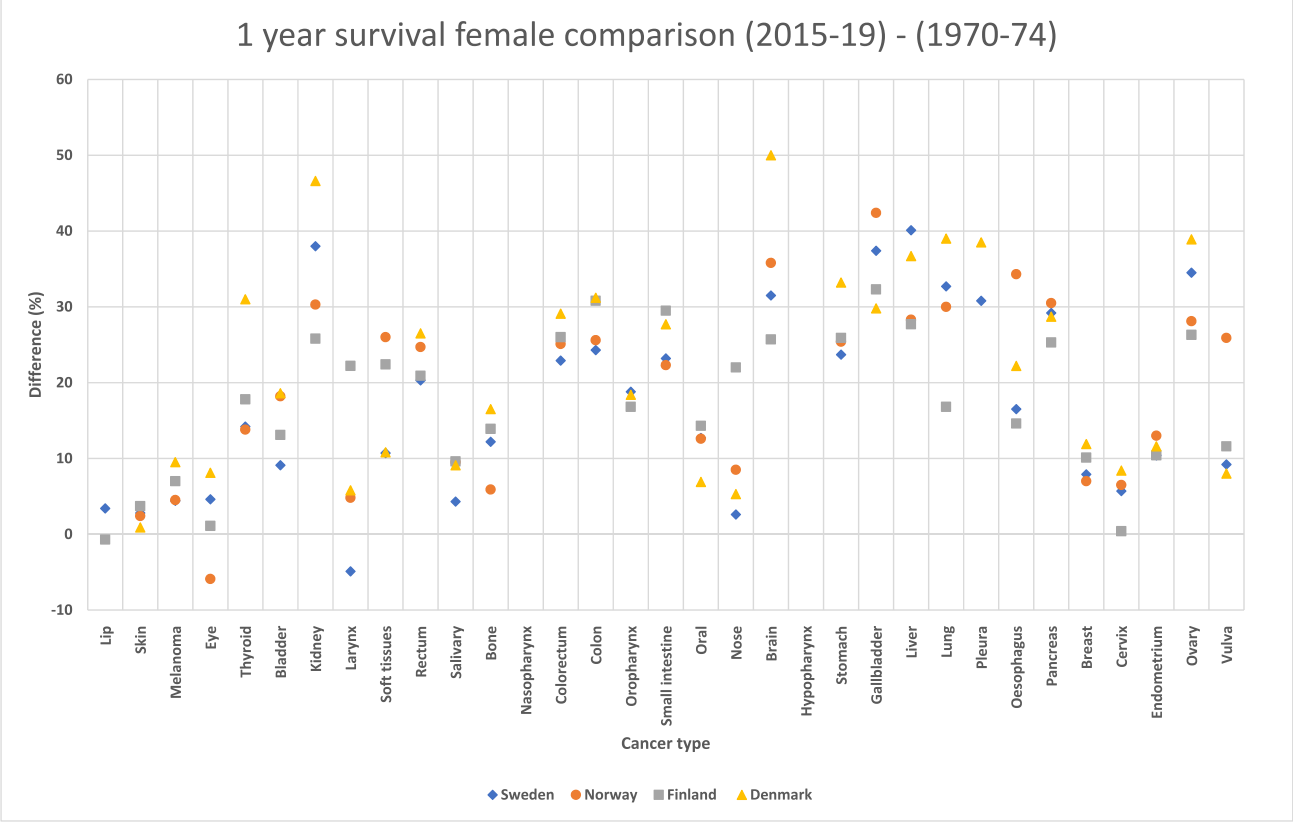

Fig. 4. Difference in 1-year relative survival (in % units) for Nordic women between 1970-74 and 2015–19.

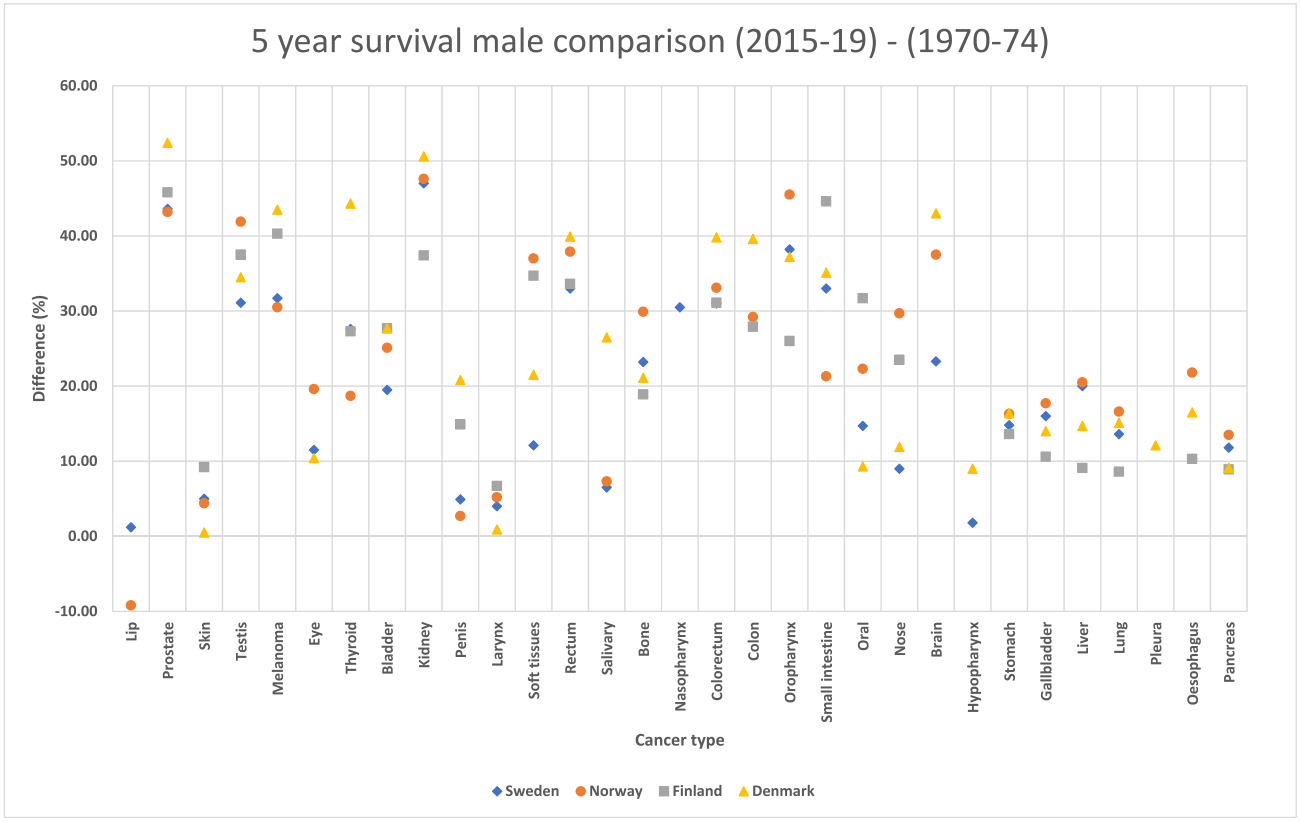

Fig. 5. Difference in 5-year relative survival (in % units) for Nordic men between 1970-74 and 2015–19.

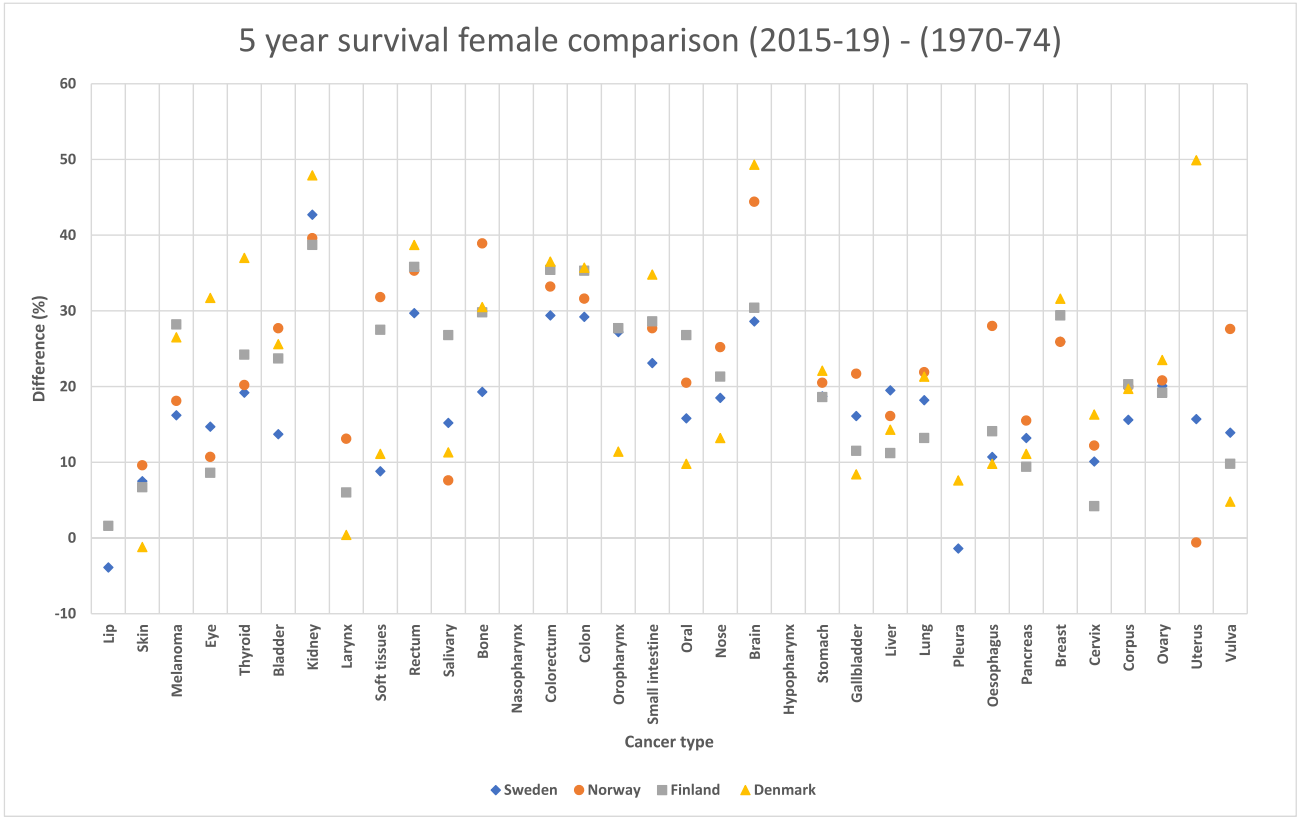

Fig. 6. Difference in 5-year relative survival (in % units) for Nordic women between 1970-74 and 2015–19.

caners, DK had 12, NO 11, FI 4 and SE 1 highest increases.

4. Discussion

We showed here, using the high-quality NORDCAN database, the up-to-date (2015–19) 1- and 5-year survival figures for solid cancers, and a 50-year trend in survival. The NORDCAN data originate from the nation-wide cancer registries from countries where health care has been available to the population at large with minimal costs, thus described a 'real-world' experience for the four countries differing in their economic resources. The results showed that the differences between countries were not large but NO, with the largest resources in health care, particularly in the last decades, had the best survival in almost half of all cancers while FI was able to claim best survival in a few cancers. The NO top ranking was not random because there was sex concordance for eight cancers, and these included some of the most fatal cancers of the gallbladder, lung, oesophagus and pancreas. A competitive ranking of NO survival data has been observed also in previous studies [8]. DK was able to match NO in the highest ranks among cancers in 5-year survival between 1970–74 and 2015–19, which is probably explained by the historical survival disadvantage in DK compared with the other Nordic countries [10,19]. The results showed a consistent survival advantage in bladder cancer for men, and in melanoma and in cancers of the skin, brain and lung for women; additionally in three of four countries survival was significantly better for women in colorectal, colon, oral and stomach cancers. The female advantage in lung cancer has been reported before and in brain cancer the likely reason is the higher proportion of indolent meningiomas in women [13,20].

Survival trends are a key measure of success in cancer control, but they have to be considered with background data on incidence and mortality [21]. Changes in incidence may imply that new risk factors are introduced (such as obesity and physical inactivity) or old risk factors diminish their impact (*Helicobacter pylori* and tobacco smoking) or that diagnostic practices have changed (prostate and breast cancer). However, the historical incidence trends in common cancers have been largely similar in the Nordic countries with some exceptions, such as male lung cancer for which rates in DK and FI have been much higher than those in SE [22,23].

The results from the last period showed that solid cancers display essentially three types of survival patterns (Figs. 1 and 2). The first includes cancers of very good survival, with both 1- and 5-year survival reaching ~90%, and features common cancers of the breast and prostate, as well as melanoma. The second pattern, which includes the largest number of cancers, showed 1-year survival of over 80% and a drop of 10–20 % units in 5-year survival; these include colorectal, bladder, kidney, cervical and endometrial cancers. Ovarian cancer was part of this group but it displayed a high decrease in survival before year 5. The third group consisted of eight fatal cancers, sharing poor 1- (below 60%) and 5-year (around 20%) survival in men and women.

The 50-year improvement in 1-year survival was largest (30–50% units) in kidney, brain, gallbladder and liver cancers, but it was also respectable (~30%) in colon, small intestinal, lung, pleural, pancreas and ovarian cancers (Figs. 3 and 4). Improvements in 5-year survival were highest (40–50 % units) in prostate and kidney cancers but remained at 10–20 % units for the eight fatal cancers (Figs. 5 and 6). Even if the latter figures do not sound encouraging, they have to be contrasted to the nil survival 50 years ago [24].

Survival time (1- or 5-year) may have important clinical implications. Patients surviving 1 year include those who were cured, those who were about to relapse but had not yet done so, and those who are alive with advanced disease. In contrast, for most tumour types, 5-year survival correlates with cure rates, as few patients with metastatic disease survive 5 years despite improvements in therapy [9]. However, there are some notable exceptions to these general principles. For example, nowadays over 30% of patients with metastatic prostate or breast cancer are alive with disease 5 years since initial diagnosis; for colorectal cancer, the proportion is 15% (US white population, SEER 17, relative survival by stage, 2012–2018; https://seer.cancer.gov/canques/survival.html). Also in other tumour types, recurrence can occur after the 5 years mark and relative survival reaching the level in the background population takes more than 5 years for most cancers [25].

Improving imaging methods have contributed to earlier detection in many cancers, which in turn would increase 1-year survival, as well as 5-year survival [26]. This can happen in at least two ways. Earlier diagnosis will increase the length of survival regardless of treatment, as it allows the tumour to be found earlier in the natural history of the disease. The second way of earlier diagnosis can improve survival is by allowing treatments (e.g. surgery, adjuvant therapies) that would not have been possible at a later stage. Millions of cancer patients have been cured by earlier diagnosis allowing curative treatment with, for example, surgery, radiotherapy, chemoradiation or even chemotherapy in some cases. Finally, smaller tumours may respond better or longer

to many medical therapies. The UK task force on 'Less Survivable Cancers', considering improving survival in the most fatal cancers, emphasised the role of early diagnosis [27].

Therefore, comparing the difference between 1- and 5-year survival may provide relevant insight into the causes of survival improvements, whether newer therapies or earlier detection. Kidney and brain cancers, belonging to the intermediary survival group, showed large improvements both in 1-year and 5-year survival, suggesting earlier detection and therapeutic advances [28]; however, for brain cancer increasing proportions of the indolent meningioma are likely to contribute to the favourable survival [13]. Testis cancer and melanoma were examples of cancers where 5-year survival increased more than 1-year survival and both treatment (chemotherapy in testicular cancer and surgery in melanoma) and early detection (melanoma) are probably playing a role. The fatal cancers were examples of those where 1- year survival improved more than 5-year survival probably because of earlier detection helped survival for 1 year, but no cure was available for metastatic disease [29,30].

Survival is critically dependent on the stage of cancer at diagnosis, but the NORDCAN database lacks such details. However, comparability of stage data over a long period may anyway be problematic (because of changes in practices and methods used in staging at diagnosis) and most important for the present comparison is diagnostic accuracy, which has been generally good for Nordic cancer registries [31]. As these registries are the oldest national cancer registries in the world, country-wise survival analysis over a half century cannot be conducted anywhere outside the Nordic countries. Survival data to the end of 2019 allow capture of the most up-to-date survival results.

In conclusion, the analysis over a half-century confirms the progress in 'real-world' cancer control, and in about two-thirds of solid cancers (and 84% of patients) 5-year survival is >60%. The challenge remains cancer metastases for which best remedy is early detection by imaging or biomarkers before metastases spread from the primary tumour. Although in at least some cancers, novel therapies such as immunotherapy may offer hope for treatment of metastatic disease, but currently, a minority of patients benefit further advances are needed. Since only a minority of cancer cases are hereditary, it can be concluded that cancer is mainly an environmental disease for which prevention is an effective remedy [32].

Author contributions

Design: KH.

Acquisition of data: JH.

Statistical analysis and interpretation: KH, AH, JH, AF.

Manuscript writing: KH and all other authors.

Approval of the final text: All authors.

Aggregated data from a publically accessible database were used posing no ethical issues.

Funding sources

Supported by the European Union's Horizon 2020 research and innovation programme, grant No 856620 (Chaperon), Jane and Aatos Erkko Foundation, Sigrid Juselius Foundation, Finnish Cancer Organizations, University of Helsinki, Helsinki University Central Hospital, Novo Nordisk Foundation, Päivikki and Sakari Sohlberg Foundation.

Conflict of interest statement

A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.08.015.

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